PATENT Customer No. 22,852 Attorney Docket No. 3495,0187-00

--This is a continuation application of PCT/EP98/05113, filed August 12, 1998, which claims the benefit under 35 U.S.C. § 119(e) of U.S. Provisional Application Nos. 60/055,615 and 60/065,236, filed August 14, 1997, and November 13, 1997, respectively.--

IN THE CLAIMS:

Please delete claims 6 and 7 without prejudice or disclaimer.

Please amend the claims as follows:

- 1. (Amended Two Times) A method for *in vivo* delivery of a fusion protein into the central nervous system (CNS), comprising administering to a human or an animal a fusion protein having a first protein comprising a non-toxic, proteolytic fragment of tetanus toxin (TT) recombinantly fused to a second protein, wherein the non-toxic, proteolytic fragment of tetanus toxin comprises a fragment C and at least the 11 amino acid residues of fragment B that immediately precede the amino terminus of fragment C, and wherein said fusion protein undergoes *in vivo* retrograde axonal transport and transynaptic transport in the CNS of the human or animal.
- 2. (Amended) The method according to claim 1, wherein the fusion protein is administered into a muscle.
- 3. (Amended) The method according to claim 2, wherein the fusion protein is administered into a muscle in the vicinity of a neuromuscular junction.
- 5. (Amended) The method according to claim 1, wherein the fusion protein is administered into neuronal cells.

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FINNEGAN
HENDERSON
FARABOW
GARRETT&
DUNNER LLP
1300 | Street, NW
Washington, DC/ 20005
2024084000

Fax 202.408.4400 Mary Finnegan.com

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- 8. (Amended) The method according to claim 1, wherein the second protein is selected from the group consisting of protein SMN, BDNF (Brain-derived neurotrophic factor), NT-3 (Neurotrophin-3), NT-4/5, GDNF (Glial cell-line-derived neurotrophic factor), IGF (Insulin-like growth factor), PNI (protease nexin I), SPI3 (Serine Protease Inhibitor protein), ICE (Interleukin-1β converting enzyme), BcI-2, GFP (green fluorescent protein), an endonuclease, an antibody, or a drug specifically directed against neurodegenerative diseases.
- 9. (Amended) The method according to claim 8, wherein the composition comprises a combination of at least two of said second proteins.
- 10. (Amended) The method according to claim 8, wherein the second protein is located upstream from the fragment of tetanus toxin.
- 11. (Amended) The method according to claim 8, wherein the second protein is located downstream from the fragment of tetanus toxin.
- 31. (Amended Two Times) A method for treating a central nervous system (CNS) disease comprising:

administering to a patient in need thereof a composition comprising a fusion protein, wherein the fusion protein comprises a first protein comprising a non-toxic, proteolytic fragment of tetanus toxin (TT) recombinantly fused to a second protein, wherein the non-toxic, proteolytic fragment of tetanus toxin comprises a fragment C and at least the 11 amino acid residues of fragment B that immediately precede the amino terminus of fragment C, and wherein the fusion protein undergoes *in vivo* retrograde axonal transport and transynaptic transport when administered to the patient.



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FINNEGAN HENDERSON FARABOW GARRETT& DUNNER LLP

1300 I Street, NW Washington, DC 20005 202.408.4000 Fax 202.408.4400 www.finnegan.com

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Please add the following new claims.

- --32. (New) The method according to claim 8, wherein the endonuclease is I-Scel or CRE.
- 33. (New) The method according to claim 8, wherein the neurodegenerative disease is latero spinal amyotrophy (LSA).
- 34. (New) The method according to claim 31, wherein the central nervous system disease is a neurodegenerative disease or a motoneuron disease.
- 35. (New) The method according to claim 34, wherein the neurodegenerative disease or the motoneuron disease is amyotrophy lateral sclerosis, spinal muscular atrophy, or a neurodegenerative lysosomal storage disease.
- 36. (New) The method according to claim 1 or 31, wherein the fusion protein comprises an amino acid sequence comprising SEQ ID NO:16.
- 37. (New) The method according to claim 1 or 31, wherein the non-toxic, proteolytic fragment of tetanus toxin consists of a fragment C and the 11 amino acid residues of fragment B that immediately precede the amino terminus of fragment C.--

<u>REMARKS</u>

Applicants respectfully request reconsideration and further examination in view of the following remarks.

Claims 1-5 and 8-37 are pending in this application. Claims 12-30 stand withdrawn from consideration as being directed to a non-elected invention. Claims 6 and 7 have been deleted without prejudice or disclaimer.

Claims 1-5, 8-11, and 31 have been amended as discussed in further detail



FINNEGAN HENDERSON FARABOW GARRETT& DUNNER LLP

1300 I Street, NW Washington, DC 20005 202.408.4000 Fax 202.408.4400 www.finnegan.com